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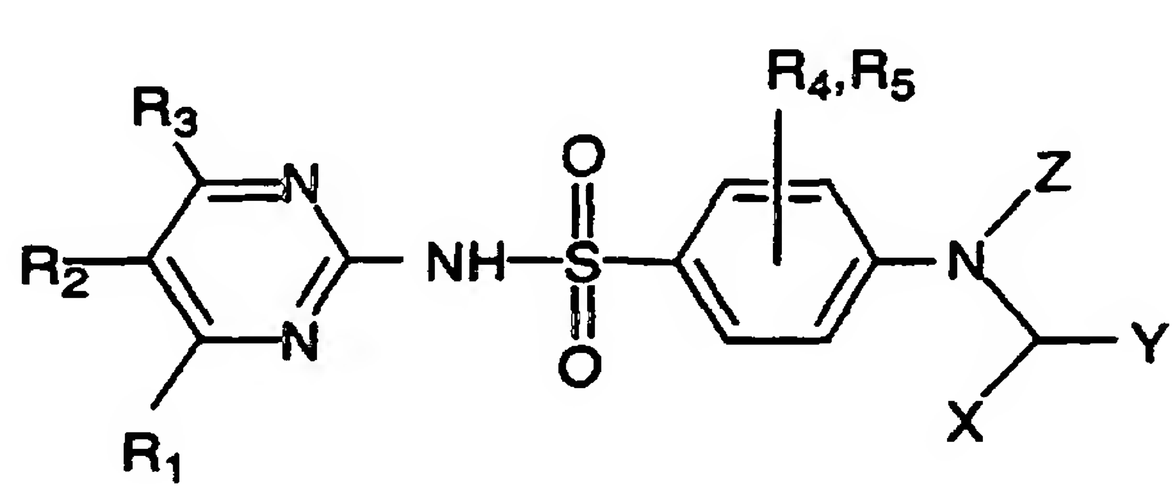
(54) Title: COMPOUNDS USEFUL FOR TREATMENT OR PREVENTION OF DISEASE MEDIATED BY ALPHA-2B-ADRENOCEPTOR



(I)

(57) Abstract: The invention relates to compounds of formula (I) or a pharmaceutically acceptable salt thereof wherein R_1, R_2, R_3, R_4 and R_5 are independently of each other H, a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen; X is H, a straight or branched alkyl chain with 1 to 4 carbon atoms, phenyl, -OH or =O; Z is H, acetyl, $-CH_2-Ph-O-CF_3$ or $CH_2-Ph-CF_3$, Y is a ring structure optionally linked to formula (I) with an alkyl chain having one or two carbon atoms. This invention further relates to the use of said compounds for the manufacture of a pharmaceutical preparation useful for the treatment or prevention of a disease mediated by the alpha-2B-adrenoceptor in a mammal.

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COMPOUNDS USEFUL FOR TREATMENT OR PREVENTION OF DISEASE MEDIATED BY ALPHA-2B-ADRENOCEPTOR

The present invention relates to the use of selective alpha-2B-adrenoceptor antagonists for the manufacture of a pharmaceutical preparation useful for the treatment or prevention of diseases mediated by the alpha-2B-adrenoceptor in mammals.

BACKGROUND OF THE INVENTION

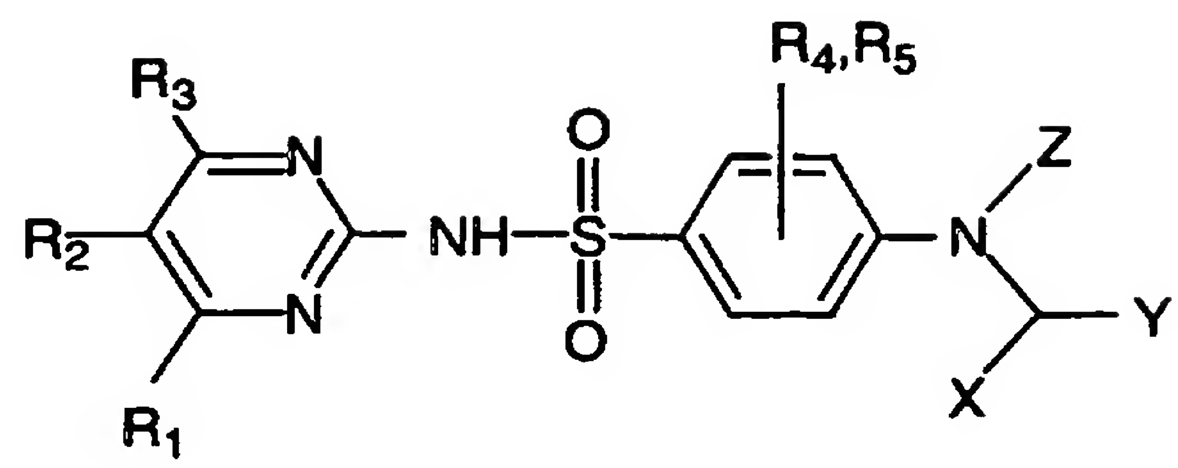
The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference.

It is known that alpha-2B-adrenoceptors mediate vascular contractions. Therefore, alpha-2B-antagonists are useful in the treatment or prevention of diseases involving vascular contraction. It has also been found that certain individuals have a genetic polymorphism in the alpha-2B-adrenoceptor gene. It has been observed that the alpha-2B-adrenoceptor protein in some subjects has a deletion of 3 glutamates from the glutamic acid repeat element of 12 glutamates (amino acids 297–309), in an acid stretch of 17 amino acids, located in the third intracellular loop of the receptor polypeptide (WO 01/29082; Heinonen et al., 1999).

OBJECTS AND SUMMARY OF THE INVENTION

An object of this invention is to provide compounds useful for the treatment or prevention of a disease mediated by the alpha-2B-adrenoceptor in a mammal.

Thus this invention concerns a novel compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof.

R_1, **R_2**, **R_3**, **R_4** and **R_5** are independently of each other H, a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen;

X is H, a straight or branched alkyl chain with 1 to 4 carbon atoms, phenyl or -OH;

Z is H, acetyl, $-CH_2$-Ph-O-CF_3 or $-CH_2$-Ph-CF_3, where Ph is phenyl;

Y is a ring structure optionally linked to formula (I) with an alkyl chain having

a) phenyl optionally mono- or disubstituted and each substituent is independently selected from the group consisting of a halogen, a straight or branched alkyl or alkoxy chain with 1 to 4 carbon atoms, a halogen substituted methyl or methoxy group, a nitrile, an amide, amino, or a nitro group;

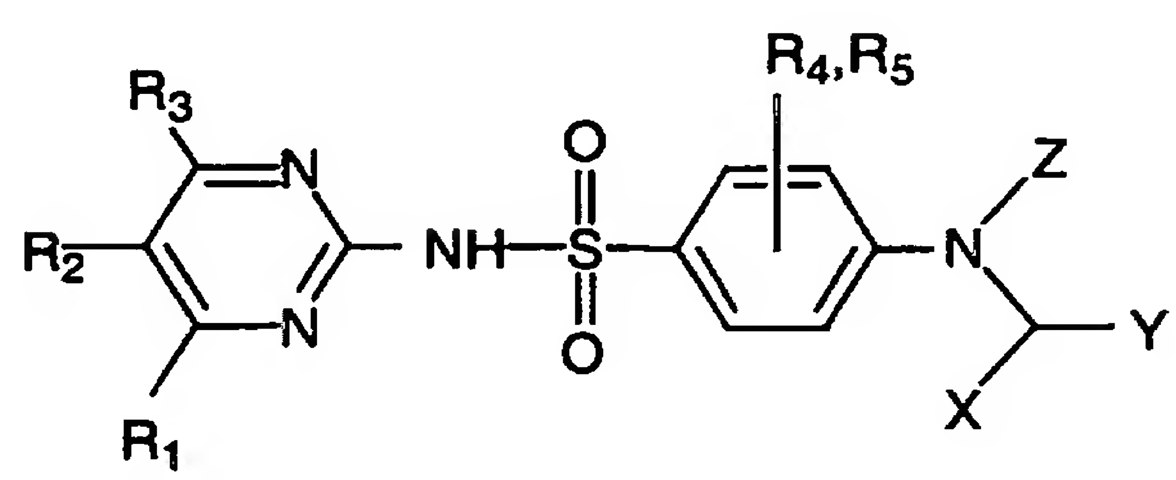
b) 2-benzimidazolyl, 2-imidazolyl, or 2- or 3-indolyl, wherein one N optionally has a substituent that is a straight or branched alkyl or alkoxy chain with 1 to 4 carbon atoms, or benzyl; and wherein the 2-benzimidazolyl, 2-imidazolyl, or 2- or 3-indolyl is optionally mono- or disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen;

(c) pyridinyl optionally mono- or disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen; or

(d) naphthyl optionally mono- or disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen.

The following previously known compounds are excluded: 4-[(*1H*-benzimidazol-2-ylmethyl)-amino]-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide (Kumar & Reddy, 1985), *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-methyl-1*H*-benzimidazol-2-ylmethyl)-amino] -benzenesulfonamide (No 653716, ChemBridge Corporation, 16981 Via Tazon, Suite G, San Diego CA 92127) and *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-ethyl-1*H*-benzimidazol-2-ylmethyl)-amino]-benzenesulfonamide (No AE-848/34956037, SPECS and BioSPECS B. V., Fleminglaan 16, 2289 CP Rijswijk, The Netherlands) and *N*-(4-methyl-2-pyrimidinyl)-4-[(1*H*-benzimidazol-2-ylmethyl)-amino]-benzenesulfonamide (Farag & El-Mouafi & Khalifa, 1991).

This invention further concerns use of compounds of formula (I)



(I)

or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical preparation useful for the treatment or prevention of a disease mediated by the alpha-2B-adrenoceptor in a mammal wherein

R_1 , **R_2** , **R_3** , **R_4** and **R_5** are independently of each other H , a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen;

X is H , a straight or branched alkyl chain with 1 to 4 carbon atoms, phenyl, -OH or =O ;

Z is H, acetyl, $-CH_2-Ph-O-CF_3$ or $-CH_2-Ph-CF_3$, where Ph is phenyl;

Y is a ring structure optionally linked to formula (I) with an alkyl chain having one or two carbon atoms, wherein the ring structure is

a) phenyl optionally mono- or disubstitued and each substituent is independently selected from the group consisting of a halogen, a straight or branched alkyl or alkoxy chain with 1 to 4 carbon atoms, a halogen substituted methyl or methoxy group, an acetyl, a nitrile, an amide, amino, or a nitro group;

b) 2-benzimidazolyl, 2-imidazolyl, or 2- or 3-indolyl, wherein one N optionally has a substituent that is a straight or branched alkyl or alkoxy chain with 1 to 4 carbon atoms, or benzyl; and wherein the 2-benzimidazolyl, 2-imidazolyl, or 2- or 3-indolyl is optionally mono- or disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen;

(c) pyrimidyl optionally mono- or disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen; or

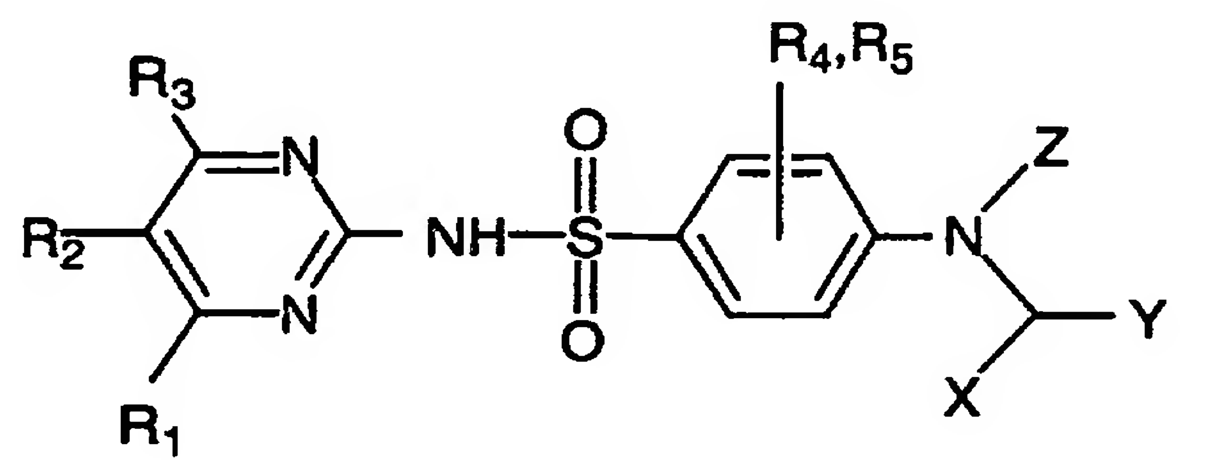
(d) naphthyl optionally mono- or disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen.

The following compounds previously known to be selective alpha-2B-adrenoceptor antagonists are excluded: *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-methyl-1*H*-benzimidazol-2-ylmethyl)-amino] -benzenesulfonamide (No 653716, ChemBridge Corporation, 16981 Via Tazon, Suite G, San Diego CA 92127), *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-ethyl-1*H*-benzimidazol-2-yl-methyl)-amino] -benzenesulfonamide (No AE-848/34956037, SPECS and BioSPECS B. V., Fleminglaan 16, 2289 CP Rijswijk, The Netherlands) and *N*-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-4-ethoxy-benzamide (No AF-

399/36012031, SPECS and BioSPECS B. V., Fleminglaan 16, 2289 CP Rijswijk, The Netherlands).

DETAILED DESCRIPTION OF THE INVENTION

Preferred compounds of the invention are compounds of formula (I)



(I),

as defined in the preceding summary or pharmaceutically acceptable salts thereof wherein $\mathbf{R_1}$ and $\mathbf{R_3}$ are methyl and $\mathbf{R_2}$, $\mathbf{R_4}$ and $\mathbf{R_5}$ are H.

In some preferable compounds **X** is H, **Y** is a phenyl optionally mono- or disubstituted with a straight or branched alkoxy group and **Z** is H. Compounds fulfilling all of the aforementioned characteristics and wherein said phenyl is substituted and said alkoxy substituent is methoxy are 4-(2,4-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(3-methoxybenzylamino)-benzenesulfonamide, 4-(3,5-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, 4-(2,5-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide and *N*-(4,6-dimethylpyrimidin-2-yl)-4-(2-methoxybenzylamino)-benzenesulfonamide.

In other preferred compounds **X** is H, **Y** is a phenyl optionally mono- or disubstituted with a straight or branched alkyl and/or a halogen and **Z** is H. These comprise compounds such as 4-benzylamino-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(2-methylbenzyl-

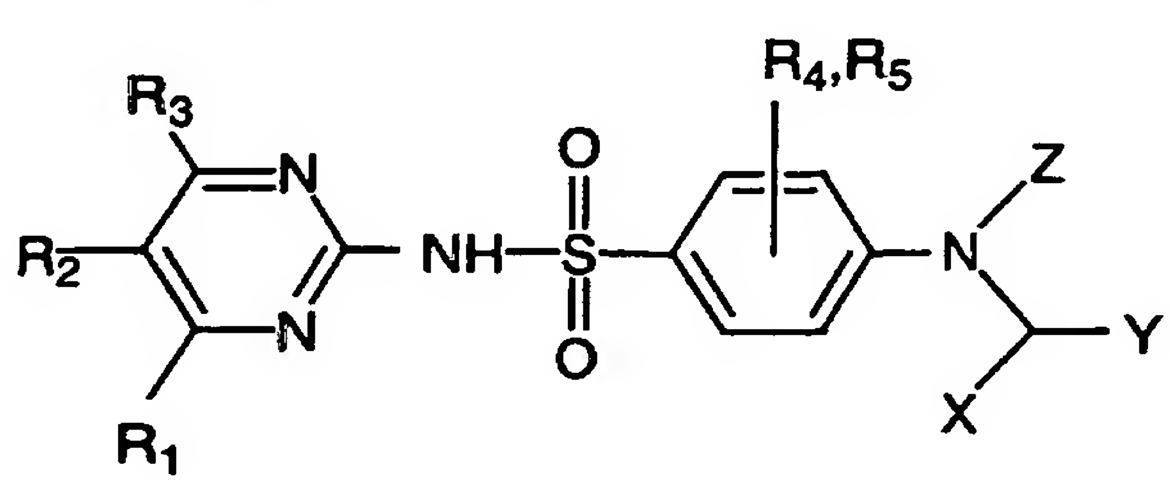
amino)-benzenesulfonamide, 4-(2,4-dimethylbenzylamino)-*N*-(4,6-dimethyl-pyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(3-methyl-benzylamino)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(4-methyl-benzylamino)-benzenesulfonamide, 4-(2,5-dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, 4-(2,6-dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, 4-(4-bromobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide and 4-(2,6-dichlorobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide.

Further preferred compounds are *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-ethyl-1*H*-indol-3-ylmethyl)-amino]-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-isobutyl-1*H*-benzimidazol-2-ylmethyl) -amino] -benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(1-phenylethylamino)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[2-(2-methoxyphenyl)-ethylamino]-benzenesulfon-

benzenesulfonamide.

According to one embodiment of the invention the compound is N-(4-methyl-2-pyrimidinyl)-4-[[(1-methyl-1H-benzimidazol-2-yl)-methyl]amino]-benzenesulfon-amide.

The invention also relates to the use of selective alpha-2B-adrenoceptor antagonists of formula (I)



(I),

as defined in the preceding summary, or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical preparation.

In many preferable compounds to be used $\mathbf{R_1}$ and $\mathbf{R_3}$ are typically methyl and $\mathbf{R_2}$, $\mathbf{R_4}$ and $\mathbf{R_5}$ are typically H.

In some compounds preferably used **X** is H, **Y** is a phenyl optionally mono- or disubstituted with a straight or branched alkoxy group and **Z** is H. Especially preferable for use are compounds in which said phenyl is substituted and said alkoxy substituent is methoxy. Such compound comprise 4-(2,4-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(3-methoxybenzylamino)-benzenesulfonamide, 4-(3,5-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, 4-(2,5-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide and *N*-(4,6-dimethylpyrimidin-2-yl)-4-(2-methoxybenzyl-amino)-benzenesulfonamide.

In other compounds preferably used **X** is H, **Y** is a phenyl optionally mono- or disubstituted with a straight or branched alkyl and/or a halogen and **Z** is H. Such compound comprise 4-benzylamino-*N*-(4,6-dimethylpyrimidin-2-yl)-benzene-sulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(2-methylbenzylamino)-benzene-sulfonamide, 4-(2,4-dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(3-methylbenzylamino)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(4-methylbenzylamino)-benzenesulfonamide, 4-(2,5-dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, 4-(2,6-dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, 4-(4-bromobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide and 4-(2,6-dichlorobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide.

Further preferred compounds to be used comprise 4-[(1*H*-benzimidazol-2-ylmethyl)-amino]-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-ethyl-1*H*-indol-3-ylmethyl)-amino]-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-isobutyl-1*H*-benzimidazol-2-ylmethyl)-amino] -benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(1-phenylethylamino)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[2-(2-methoxyphenyl)-ethylamino]-benzenesulfonamide and *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(naphthalen-2-ylmethyl)-amino]-benzenesulfonamide.

Alpha-2B-adrenoceptor antagonists are useful in the treatment and/or prevention of many diseases.

Individuals having a deletion in the alpha-2B-adrenoceptor protein (WO 01/29082; Heinonen et al., 1999), particularly the deletion/deletion genotype (D/D genotype)

alpha-2B-adrenoceptor antagonists. These individuals have a deletion of 3 glutamates from the glutamic acid repeat element of 12 glutamates (amino acids 297–309), in an acid stretch of 17 amino acids, located in the third intracellular loop of the receptor polypeptide.

It has been found that in a population-based cohort of Finnish middle-aged men that subjects with a D/D genotype of the alpha-2B-adrenoceptor gene have a significantly elevated risk for acute myocardial infarction (AMI) in a five-year follow-up study. The risk for AMI was increased in subjects who had no previously diagnosed coronary heart disease (CHD) at the study outset. Therefore, it has been postulated that the D/D genotype is related to an impaired capacity to down-regulate alpha-2B-adrenoceptor function during sustained receptor activation. Therefore, alpha-2B-adrenoceptors are believed to be involved in the pathogenesis of a significant fraction of all cases of AMI, especially in subjects

with the D/D genotype, but also in I/D and I/I subjects (I means "insertion" and stands for the "normal" allele).

The alpha-2B-adrenoceptor antagonists as disclosed in this invention would be particularly useful in the treatment or prevention of coronary heart diseases. As examples can be mentioned

a) Acute AMI

If alpha-2B-adrenoceptor dependent vasoconstriction is a causative factor in some cases of AMI, then antagonism of these receptors should restore coronary circulation and reduce the ischemic myocardial damage.

b) Unstable angina pectoris

An alpha-2B-adrenoceptor antagonist will relieve the vasoconstrictive component in the sustained ischemic episode, thus alleviating the symptoms

c) Prinzmetal's variant form of angina pectoris

Vasoconstriction is a key factor in the pathogenesis of Prinzmetal's angina, and an alpha-2B- adrenoceptor antagonist may resolve and prevent attacks.

d) Other forms of chronic angina pectoris and CHD

An alpha-2B-adrenoceptor antagonist will help to alleviate the vasoconstrictive component in all types of CHD, providing both symptomatic relief and protection from AMI. A general reduction in vascular tone will contribute to this by reducing venous return, cardiac workload and oxygen consumption (a nitrate-type effect; see below).

e) Prevention of restenosis after coronary angioplasty in cases where vasoconstriction plays a role in restenosis.

Furthermore, the alpha-2B-adrenoceptor antagonists as disclosed in this invention would be useful in the treatment or prevention of essential hypertension, especially

in subjects with increased sympathetic activity and a hyperdynamic circulatory system.

In the study mentioned above, the D/D variant of the alpha-2B-adrenoceptor gene was not clearly associated with blood pressure. The inventors believe that this was due to two main factors, 1) antihypertensive treatment, and 2) complex regulation of systemic blood pressure. In another study (Heinonen et al.), it was observed that the D/D genotype was associated with reduced basal metabolic rate and reduced heart rate. These associations probably reflect increased vascular resistance in these subjects.

In transgenic mice with targeted inactivation of the alpha-2B-adrenoceptor gene, intravenously administered alpha-2-adrenoceptor agonists fail to induce the characteristic blood pressure elevation, which is seen in normal animals and also in humans after large doses of such drugs (Link et al., 1996). The hypotensive effect of these drugs was markedly accentuated. This demonstrates that alpha-2B-adrenoceptors mediate vascular contraction. Thus, an antagonist should reduce blood pressure. This effect has not been seen with alpha-2B-non-selective alpha-2-adrenoceptor antagonists, because antagonism of alpha-2A-adrenoceptors increases sympathetic outflow, cardiac output and blood pressure. In mice with dysfunctional alpha-2A-adrenoceptors, alpha-2-adrenoceptor agonists caused an accentuated hypertensive response and no hypotension (MacMillan et al., 1996).

An alpha-2B-adrenoceptor antagonist is postulated to have favourable effects in hypertensive subjects through their effects on renal function, muscle blood flow, and also on vascular resistance in other vascular beds. The anti-AMI effect of such a drug will be an additional benefit, as hypertension is a significant risk factor for AMI. This protection is due to three factors: 1) a reduction in systemic blood pressure, 2) decreased risk of coronary vasoconstriction, and 3) a nitrate-like effect on venous return, myocardial workload and oxygen consumption.

Moreover, the alpha-2B-adrenoceptor antagonists as disclosed in this invention would be useful in the treatment or prevention of other vascular diseases. Specifically, benefits can be expected in the treatment or prevention of

- vasoconstriction and hypoxic brain damage subsequent to subarachnoid haemorrhage,
- migraine,
- Raynaud's disease and cold intolerance,
- pre-eclampsia,
- male erectile dysfunction, and
- obesity and the metabolic syndrome.

The last mentioned effect is due to the fact that reduced muscle blood flow and reduced basal metabolic rate contribute to the development of obesity and hypertension. An alpha-2B-adrenoceptor antagonist will, by increasing the muscle

favourable direction.

The alpha-2B-adrenoceptor antagonists disclosed in this invention are also useful in anaesthesia and analgesia to potentiate the clinical efficacy of alpha-2-adrenoceptor agonists, which are not selective for the alpha-2B-adrenoceptor subtype. By blocking the vasoconstriction induced by these agonists, a simultaneously administered alpha-2B-adrenoceptor antagonist will allow the use of larger doses of said agonists, up to anaesthetic dose levels which have not previously been possible in man, only in veterinary anaesthetic practice.

EXPERIMENTAL SECTION

Human alpha-2-adrenoceptor binding affinity

The affinity of test compounds for the three human α_2-adrenoceptor subtypes (α_{2A}, α_{2B} and α_{2C}) was determined in competition binding assays with ^{3}H-rauwolscine. The biological material for these experiments consisted of membranes from Shionogi S115 cells stably transfected with any of the three human α_2 subtypes (Marjamäki et al. 1992). Membrane (5–10 μg of total protein per sample) and 1–2 nM ^{3}H-rauwolscine (specific activity 78 Ci/mmol) were incubated in 50 mM KH_2PO_4, pH 7.5 with 6 concentrations of the compounds. Each concentration was run in duplicate. Non-specific binding was defined by 100 μM oxymetazoline and corresponded to 5–15% of total binding. After 30 min at room temperature, incubations were terminated by rapid vacuum filtration through GF/B glass fiber filter and three 5 ml washes with ice-cold incubation buffer. The filters were then dried, impregnated with scintillate and their radioactivity was measured by scintillation counting. The analysis of the experiments was carried out by non-linear least square curve fitting. Experimentally determined IC50 values were converted to Ki's by making use of the Cheng-Prusoff equation (Cheng and Prusoff, 1973). Experiments were repeated a minimum of three times.

Table 1: Human α_2-adrenoceptor subtypes binding affinities. Data is presented as Ki's in nM (Mean ± SEM).

Compound	alpha-2A	alpha-2B	alpha-2C
A	>13000	160 ± 20	>30000
B	>4500	34 ± 2	>10000
C	2000 ± 400	10 ± 2	>10000
D	>10000	440 ± 70	>10000
E	>5100	20 ± 4	>10000

F	>4300	43 ± 7	>10000
G	2200 ± 600	32 ± 5	>10000
H	>30000	8000 ± 500	>30000

Results expressed in the form of " > " means that no numerical values for Ki's could be established due to lack of displacement or due to incomplete competition curves. However, the experimental data indicated that, at a minimum, the Ki's must be larger than the numbers given.

Antagonist activity on human alpha-2-adrenoceptor subtypes

Antagonist potencies were determined as the ability of test compounds to competitively inhibit epinephrine-stimulated ^{35}S-GTPγS binding to G proteins (Tian et al., 1993; Wieland and Jakobs, 1994; Jasper et al., 1998) in membranes of CHO cells stably transfected with one of the three human α_2 subtypes (Pohjanoksa et al., 1997; Marjamäki et al., 1998). Membranes (2–6 μg of protein per sample) and 12 concentrations of test compound were preincubated for 30 min with a fixed concentration fo epinephrine (5 μM for α_{2A},, 15 μM for α_{2B}, 5 μM for α_{2C}) in 50 mM Tris, 5 mM $MgCl_2$, 150 mM NaCl, 1 mM DTT, 1 mM EDTA, 10 μM GDP, 30 μM ascorbic acid, pH 7.4 at room temperature. Binding of radiolabel was started by the addition of trace amounts of ^{35}S-GTPγS (0.08–0.15 nM, specific activity 1250 Ci/mmol) to the incubation mixture. After an additional 60 min at room temperature, the incubation was terminated by rapid vacuum filtration through glass fibre filter. Filters were washed three times with 5 ml ice cold wash buffer (20 mM Tris, 5 mM $MgCl_2$, 1 mM EDTA pH 7.4 at room temperature), dried and counted for radioactivity in a scintiallation counter. Analysis of experiments was carried out by non-linear least square fitting. Results are based on a minimum of three experiments.

Table 2: Antagonist effect on human α_2-adrenoceptor subtypes. Data is presented as KB's in nM (Mean ± SEM).

Compound	alpha-2A	alpha-2B	alpha-2C
B	14500 ± 3600	75 ± 9	5700 ± 700
C	5400 ± 1400	17 ± 5	6300 ± 1400
E	7900 ± 3100	29 ± 5	7300 ± 1100
F	8700 ± 1100	240 ± 60	12000 ± 2000
G	3200 ± 500	86 ± 64	4700 ± 1800

For the purpose of the invention, the alpha-2B-adrenoceptor antagonist or its pharmaceutically acceptable salt can be administered by various routes. The suitable administration forms include, for example, oral formulations; parenteral injections including intravenous, intramuscular, intradermal and subcutanous injections; transdermal or rectal administration forms. The required dosage of the compounds of the alpha-2B-adrenoceptor antagonist will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the administration route and the specific compound being employed. The suitable dose varies in the range 5 μg to 100 mg per kg body weight and day for an adult person.

EXAMPLES

Example 1

N-(4,6-Dimethylpyrimidin-2-yl)-4-[(1-ethyl-1H-benzimidazol-2-ylmethyl)-amino] -benzenesulfonamide

Step I: Alkylation of 2-hydroxymethylbenzimidazole

99.2 mg (0.67 mmol) 2-hydroxymethylbenzimidazole was dissolved in 3 ml methanol. Potassium carbonate (103.1 g, 0.75 mmol) and diethylsulfate (442 µl 3.38 mmol) were added to the reaction mixture. Solution was stirred and refluxed overnight. The reaction mixture was then evaporated to dryness and purified on silica using gradient elution (chloroform to 5% methanol in chloroform) to obtain

Step II: Chlorination of 1-ethyl-2-hydroxymethylbenzimidazole

20 mg (0.11 mmol) 1-ethyl-2-hydroxymethylbenzimidazole was dissolved in 2 ml dichloromethane. Thionyl chloride (24 µl, 0.33 mmol) was diluted 20 times with dichloromethane and the solution was added to the reaction mixture. Reaction mixture was stirred at room temperature for two hours, evaporated to dryness and washed with water to yield 1-ethyl-2-chloromethylbenzimidazole as pale yellow crystals, 36 mg (95%).

Step III: Coupling reaction between 1-ethyl-2-chloromethylbenzimidazole and sulfamethazine

32.4 mg (0,12 mmol) sulfamethazine and 36 mg (0.18 mmol) 1-ethyl-2-chloromethylbenzimidazole were dissolved in 4 ml methanol. 64 µl (0.44 mmol) triethylamine and catalytic amount of sodium iodide were added to the reaction

mixture. Solution was stirred and refluxed overnight. The reaction mixture was then evaporated to dryness, and purified on silica using gradient elution (chloroform to 5% methanol in chloroform) to provide white crystals of the title compound, 10 mg (20%). ^{1}H NMR (DMSO-d_6, 500 MHz): 7.68 (2H, m), 7.60 (1H, m), 7.52 (1H, m), 7.22 (1H, m), 7.17 (1H, m), 7.00 (1H, br, s), 6.78 (3H, m), 6.60 (1H, br, s), 4.60 (2H, m), 4.30 (2H, q, 7.2 Hz), 2.18 (6H, s), 1.28 (3H, t, 7.2 Hz); MS (ESI$^+$): m/z 437 $(M + H)^+$.

Example 2

4-[(1*H*-Benzimidazol-2-ylmethyl)-amino]-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Following the procedure outlined in Step III of example 1, but without triethylamine and substituting 1-ethyl-2-chloromethylbenzimidazole by 2-chloromethylbenzimidazole afforded the title compound with the yield of 51%. ^{1}H NMR (DMSO-d_6, 500 MHz): 7.70 (2H, m), 7.48 (2H, br, m), 7.13 (2H, m), 7.11 (1H, t, 5.8 Hz), 6.70 (3H, m), 4.52 (2H, d, 5.8 Hz), 2.21 (6H, s); MS (ESI$^+$): m/z 409 $(M + H)^+$.

Example 3

N-(4,6-Dimethylpyrimidin-2-yl)-4-[(pyridin-4-ylmethyl)-amino]-benzenesulfonamide

Following the procedure outlined in Step III of example 1 without triethylamine and substituting 1-ethyl-2-chloromethylbenzimidazole by 4-picolylchloride hydrochloride afforded the title compound with the yield of 54%. MS (ESI$^+$): m/z 392 $(M + Na)^+$, 370 $(M + H)^+$.

Example 4

<u>*N*-(4,6-Dimethylpyrimidin-2-yl)-4-[(1-isobutyl-1*H*-benzimidazol-2-ylmethyl)-amino] -benzenesulfonamide (Compound A)</u>

Following the procedure outlined in example 1, but substituting in step I ethyl bromide for isobutyl iodide, afforded the title compound with stepwise yields of 15%, 95% and 15%. ^{1}H NMR (DMSO-d_6, 500 MHz): 7.76 (2H, m), 7.70 (1H, m), 7.60 (1H, m), 7.27 (1H, m), 7.22 (1H, m), 7.15 (1H, br, t, 5.3 Hz), 6.86 (2H, m), 6.77 (1H, s), 4.65 (2H, d, 5.3 Hz), 4.13 (2H, d, 7.5 Hz), 2.27 (6H, s), 2.25 (1H, m), 0.91 (6H, d, 6.7 Hz); MS (ESI$^+$): m/z 487 $(M + Na)^+$, 465 $(M + H)^+$.

Example 5

[illegible]

<u>yl)- benzenesulfonamide</u>

Following the procedure outlined in example 1, but substituting in step I ethyl bromide for benzyl bromide, afforded the title compound with stepwise yields of 23%, 90% and 18%. ^{1}H NMR (DMSO-d_6, 500 MHz): 7.81 (2H, m), 7.52 (1H, m), 7.45 (1H, m), 7.30 (5H, m), 7.16 (2H, m), 6.75 (1H, s), 6.54 (2H, m), 6.02 (1H, br, s), 5.66 (2H, s), 5.63 (2H, s), 2.21 (6H, s); MS (ESI$^+$): m/z 521 $(M + Na)^+$, 499 $(M + H)^+$.

Example 6

<u>4-[(1-Ethyl-1*H*-benzimidazol-2-ylmethyl)-amino]-*N*-(5-methoxypyrimidin-2-yl]-benzenesulfonamide</u>

Following the procedure outlined in example 1 step III, but substituting sulfamethazine by 5-methoxysulfadiazine, afforded the title compound with the

yield of 8%. Dimethylformamide was used as a solvent and additional silica gel chromatography purification with 2:1 petrol ether:ethylacetate was needed. MS (ESI^+): m/z 461 $(M + Na)^+$, 439 $(M + H)^+$.

Example 7

4-[(1*H*-Benzimidazol-2-ylmethyl)-amino]-*N*-(pyrimidin-2-yl)-benzenesulfonamide

628 mg (3.8 mmol) sulfadiazine and 728 mg (3.0 mmol) 2-chloromethylbenzimidazole were dissolved in 10 ml 1 M NaOH. Solution was stirred and refluxed for four hours. Reaction mixture was neutralised with addition of 1 M acetic acid until product precipitated. Crystals were filtered and purified on silica using gradient elution (chloroform to 5% methanol in chloroform) to obtain the title compound as white crystals with 38% yield. ^1H NMR (DMSO-d_6, 500 MHz):

6.98 (1H, m), 6.72 (2H, m), 4.53 (2H, 5.7 Hz); MS (ESI^+): m/z 381 $(M + H)^+$.

Example 8

N-(1*H*-Benzimidazol-2-ylmethyl)-*N*-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-acetamide

18 mg (0.044 mmol) 4-[(1*H*-benzimidazol-2-ylmethyl)-amino]-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide was dissolved in 2 ml of 15% pyridine in dichloromethane. Acetyl chloride (31µl, 0.44 mmol) was diluted with 1 ml dichloromethane and solution was added to the reaction mixture. After three hours reaction mixture was washed with acidic water and organic layer was evaporated to dryness. Crystals were purified on silica using gradient elution (chloroform to 5% methanol in chloroform) to obtain white crystals with 30% yield. ^1H NMR (DMSO-d_6, 500 MHz): 7.97 (2H, m), 7.60 (2H, m), 7.48 (2H, m), 7.14 (2H, m),

6.68 (1H, s), 5.08 (2H, s), 2.18 (6H, s), 1.93 (3H, s); MS (ESI$^+$): m/z 473 (M + Na)$^+$, 451 (M + H)$^+$.

Example 9

N-(1-Acetyl-1H-benzimidazol-2-ylmethyl)-N-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-acetamide

Title compound was purified from the reaction mixture produced according to example 8 with a yield of 14%. ^{1}H NMR (DMSO-d_6, 500 MHz): 8.15 (2H, m), 7.80 (2H, m), 7.55 (2H, m), 7.48 (1H, s), 7.21 (3H, m), 5.17 (2H, s), 2.54 (6H, s), 2.03 (3H, s), 1.83 (3H, s); MS (ESI$^+$): m/z 493 (M + H)$^+$.

Example 10

4-[(1-Acetyl-1H-benzimidazol-2-ylmethyl)-amino]-N-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Following the procedure of example 8, but instead of 15% pyridine in dichloromethane only few drops of pyridine in dichloromethane were used as a solvent. Method afforded the title compound with a yield similar to that for *N*-(1*H*-benzimidazol-2-ylmethyl)-*N*-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-acetamide. MS (ESI$^+$): m/z 451 (M + H)$^+$.

Example 11

4-Benzylamino-N-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

100 mg (0.36 mmol) sulfamethazine and 70.8 µl (0.60 mmol) benzyl bromide were dissolved in 4 ml methanol. Caesium carbonate (113.4 mg, 0.35 mmol) was added and solution was refluxed overnight with stirring. The reaction mixture was then

evaporated to dryness, and purified on silica using gradient elution (chloroform to 2% methanol in chloroform) to obtain white crystals in a yield similar to that described in example 1 for step III. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.93 (2H, m), 7.31 (5H, m), 6.58 (3H, m), 4.36 (2H, s), 2.34 (6H, s); MS (ESI$^+$): m/z 369 (M + H)$^+$.

Example 12

<u>4-(4-Bromobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide</u>

Following the procedure outlined in example 11, but substituting benzyl bromide by 4-bromobenzyl bromide, afforded the title compound with a yield of 8%. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.91 (2H, m), 7.45 (2H, m), 7.19 (2H, m), 6.59 (1H, s) 6.55 (2H, m), 4.32 (2H, s), 2.34 (6H, s); MS (ESI$^+$): m/z 469 (M + Na)$^+$, 447 (M + H)$^+$.

Example 13

<u>*N*-(4,6-Dimethylpyrimidin-2-yl)-4-(2-methylbenzylamino)-benzenesulfonamide (Compound B)</u>

Following the procedure outlined in example 11, but substituting benzyl bromide by 2-methylbenzyl bromide, afforded the title compound in a yield similar to that described in example 1 for step III. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.95 (2H, m), 7.22 (4H, m), 6.58 (3H, m), 4.30 (2H, s), 2.35 (3H, s), 2.34 (6H, s); MS (ESI$^+$): m/z 405 (M + Na)$^+$.

Example 14

N-(4,6-Dimethylpyrimidin-2-yl)-4-(4-methylbenzylamino)-benzenesulfonamide

Following the procedure outlined in example 11, but substituting benzyl bromide by 4-methylbenzyl bromide, afforded the title compound in a yield similar to that described in example 1 for step III. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.92 (2H, m), 7.20 (2H, m), 7.15 (2H, m), 6.58 (3H, m), 4.31 (2H, s), 2.34 (3H, s), 2.33 (6H, s); MS (ESI^+): m/z 405 $(M + Na)^+$, 383 $(M + H)^+$.

Example 15

N-(4,6-Dimethylpyrimidin-2-yl)-4-(1-phenylethylamino)-benzenesulfonamide

Following the procedure outlined in example 11, but substituting benzyl bromide by (1-bromoethyl)-benzene, afforded the title compound with a yield of 12%. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.84 (2H, m), 7.31 (5H, m), 6.57 (1H, s), 6.46 (2H, m), 4.53 (1H, q, 6.7 Hz), 2.30 (6H, s), 1.54 (3H, d, 6.7 Hz); MS (ESI^+): m/z 405 $(M + Na)^+$, 383 $(M + H)^+$.

Example 16

N-(4,6-Dimethylpyrimidin-2-yl)-4-(2-methoxybenzylamino)-benzenesulfonamide

Following the procedure outlined in example 11, but substituting benzyl bromide by 2-methoxybenzyl bromide, afforded the title compound in a yield similar to that described in example 1 for step III. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.92 (2H, m), 7.25 (2H, m), 6.90 (2H, m), 6.59 (3H, m), 4.36 (2H, s), 3.86 (3H, s), 2.32 (6H, s); MS (ESI^+): m/z 421 $(M + Na)^+$, 399 $(M + H)^+$.

Example 17

4-(2,4-Dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Following the procedure outlined in example 11, but substituting benzyl bromide by 2,4-dimethylbenzyl bromide, afforded the title compound with a yield of 23%. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.94 (2H, m), 7.14 (1H, m), 7.03 (1H, s), 6.98 (1H, m), 6.58 (3H, m), 4.26 (2H, s), 2.34 (6H, s), 2.31 (3H, s), 2.30 (3H, s); MS (ESI$^+$): m/z 419 $(M + Na)^+$, 397 $(M + H)^+$.

Example 18

N-(4,6-Dimethylpyrimidin-2-yl)-4-(3-methylbenzylamino)-benzenesulfonamide

Following the procedure outlined in example 11, but substituting benzyl bromide by 3-methylbenzyl bromide, afforded the title compound with a yield of 10%. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.93 (2H, m), 7.23 (1H, m), 7.11 (3H, m), 6.62 (1H, s), 6.58 (2H, m), 4.31 (2H, s), 2.36 (6H, s), 2.34 (3H, s); MS (ESI$^+$): m/z 405 $(M + Na)^+$, 383 $(M + H)^+$.

Example 19

4-(2,6-Dichlorobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide (Compound **C**)

Following the procedure outlined in example 11, but substituting benzyl bromide by 2,6-dichlorobenzyl bromide, afforded the title compound with the yield of 10%. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.96 (2H, m), 7.34 (2H, m), 7.20 (1H, m), 6.71 (2H, m), 6.59 (1H, s), 4.63 (2H, s), 2.34 (6H, s); MS (ESI$^+$): 437 $(M + H)^+$.

Example 20

N-(4,6-Dimethylpyrimidin-2-yl)-4-[(naphthalen-2-ylmethyl)-amino]-benzenesulfonamide (Compound **D**)

Following the procedure outlined in example 11, but substituting benzyl bromide by 2-bromomethylnaphtalene, afforded the title compound with the yield of 20%. ^{1}H NMR (DMSO-d_6, 500 MHz): 7.85 (4H, m), 7.68 (2H, m), 7.47 (3H, m), 7.19 (1H, t, 5.8 Hz), 6.70 (1H, s), 6.66 (2H, m), 4.49 (2H, d, 5.8 Hz), 2.21 (6H, s); MS (ESI$^+$): m/z 441 $(M + H)^+$.

Example 21

N-(4,6-Dimethylpyrimidin-2-yl)-4-(3-methoxybenzylamino)-benzenesulfonamide [illegible]

Following the procedure outlined in example 11, but substituting benzyl bromide by 3-methoxybenzyl bromide, afforded the title compound with the yield of 28%. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.93 (2H, m), 6.86 (3H, m), 6.58 (3H, m), 4.33 (2H, s), 3.78 (3H, s), 2.33 (6H, s); MS (ESI$^+$): m/z 421 $(M + Na)^+$, 399 $(M + H)^+$.

Example 22

N-(4,6-Dimethylpyrimidin-2-yl)-4-(4-nitrobenzylamino)-benzenesulfonamide

Following the procedure outlined in example 11, but substituting benzyl bromide by 4-nitrobenzyl bromide, afforded the title compound with a yield lower than 1%. MS (ESI$^+$): m/z 414 $(M + H)^+$.

Example 23

N-(4,6-Dimethylpyrimidin-2-yl)-4-(4-trifluoromethylbenzylamino)-benzenesulfonamide

Following the procedure outlined in example 11, but substituting benzyl bromide by 4-trifluoromethylbenzyl bromide, afforded the title compound in a yield similar to that described in example 1 for step III. MS (ESI^+): m/z 459 $(M + Na)^+$, 437 $(M + H)^+$.

Example 24

4-[Bis-(4-trifluoromethylbenzyl)-amino]-N-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Title compound was purified from the reaction mixture produced according to example 23 with the yield of 20%. MS (ESI^+): 617 m/z $(M + Na)^+$, 595 $(M + H)^+$.

Example 25

N-(4,6-Dimethylpyrimidin-2-yl)-4-(4-trifluoromethoxybenzylamino)-benzenesulfonamide

Following the procedure outlined in example 11, but substituting benzyl bromide by 4-trifluoromethoxybenzyl bromide, afforded the title compound with a yield of 25%. MS (ESI^+): m/z 475 $(M + Na)^+$, 453 $(M + H)^+$.

Example 26

4-[Bis-(4-trifluoromethoxybenzyl)-amino]-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Title compound was purified from the reaction mixture produced according to example 25 with a yield of 15%. MS (ESI^+): m/z 649 $(M + Na)^+$, 627 $(M + H)^+$.

Example 27

4-(2,5-Dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Following the procedure outlined in example 11 without caesium carbonate and substituting benzyl bromide by 2,5-dimethylbenzyl bromide afforded the title compound with a yield of 35%. ^1H NMR ($CDCl_3$, 500 MHz): 7.95 (2H, m), 7.07 (3H, m), 6.59 (3H, m), 4.25 (2H, s), 2.33 (6H, s), 2.30 (3H, s), 2.28 (3H, s); MS (ESI^+): m/z 419 $(M + Na)^+$.

Example 28

4-(2,6-Dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Following the procedure outlined in example 11 without caesium carbonate and substituting benzyl bromide by 2,6-dimethylbenzyl bromide afforded the title compound with a yield of 25%. ^1H NMR ($CDCl_3$, 500 MHz): 7.99 (2H, m), 7.08 (3H, m), 6.62 (3H, m), 4.26 (2H, s), 2.37 (12H, m); MS (ESI^+): m/z 419 $(M + Na)^+$.

Example 29

4-(3,5-Dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Following the procedure outlined in example 11 without caesium carbonate and substituting benzyl bromide by 3,5-dimethoxybenzyl chloride afforded the title compound with a yield of 15%. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.92 (2H, m), 6.60 (1H, s), 6.58 (2H, m), 6.46 (2H, m), 6.38 (1H, m), 4.30 (2H, s), 3.76 (6H, s), 2.33 (6H, s); MS (ESI$^+$): m/z 429 $(M + H)^+$.

Example 30

4-(2,5-Dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Following the procedure outlined in example 11 without caesium carbonate and substituting benzyl bromide by 2,5-methoxybenzyl chloride afforded the title compound with the yield of 13%. Reaction time was three days. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.91 (2H, m), 6.79 (3H, m), 6.58 (3H, m), 4.33 (2H, s), 3.81 (3H, s), 3.71 (3H, s), 2.33 (6H, s); MS (ESI$^+$): m/z 429 $(M + H)^+$.

Example 31

2,6-Dichloro-*N*-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-benzamide

Following the procedure outlined in example 11, but substituting benzyl bromide by 2,6-dichlorobenzoyl chloride, afforded the title compound with almost quantitative yield. ^{1}H NMR ($CDCl_3$, 500 MHz): 8.11 (2H, m), 7.80 (2H, m), 7.33 (3H, m), 6.59 (1H, s), 2.34 (6H, s); MS (ESI$^+$): m/z 473 $(M + H)^+$, 451 $(M + H)^+$.

Example 32

4-(2-Cyanobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Following the procedure outlined in example 11, but substituting benzyl bromide by α-bromo-*o*-tolunitrile, afforded the title compound with a yield of 21%. ^1H NMR (DMSO-d_6, 500 MHz): 7.83 (1H, m), 7.71 (2H, m), 7.65 (1H, m), 7.47 (2H, m), 7.15 (1H, br, t, 5.8 Hz), 6.73 (1H, m), 6.63 (2H, m), 4.50 (2H, d, 5.8 Hz), 2.24 (6H, s); MS (ESI$^+$): m/z 416 $(M + Na)^+$, 394 $(M + H)^+$.

Example 33

4-(2,4-Dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

62 mg (0.37 mmol) 2,4-dimethoxybenzylaldehyde and 100.9 mg (0.36 mmol) sulfamethazine were dissolved in 4 ml of 1,2-dichloroethane. Acetic acid (168 µl, 2.8 mmol) was added to the reaction mixture and solution was stirred with reflux overnight. Sodium triacetoxyborohydride (162.9 mg, 0.77 mmol) was dissolved to the reaction solution and refluxing was continued for three hours. The reaction mixture was then evaporated to dryness, and purified on silica using gradient elution (chloroform to 2% methanol in chloroform) and 2:1 petrol ether:ethylacetate to obtain the title compound as white crystals with a yield of 10%. . ^1H NMR ($CDCl_3$, 500 MHz): 7.91 (2H, m), 7.13 (1H, m), 6.58 (3H, m), 6.47 (1H, m), 6.42 (1H, m), 4.53 (1H, t, 5.0 Hz), 4.30 (2H, d, 5.0 Hz), 3.82 (3H, s), 3.79 (3H, s), 2.33 (6H, s); MS (ESI$^+$): m/z 429 $(M + H)^+$.

Example 34

<u>*N*-(4,6-Dimethylpyrimidin-2-yl)-4-[(1-ethyl-1*H*-indol-3-ylmethyl)-amino]-benzenesulfonamide (Compound F)</u>

1-ethylindole-3-carboxaldehyde was prepared from alkylation reaction of indole-3-carboxaldehyde. Indole-3-carboxaldehyde (900 mg, 6.2 mmol) was dissolved in 5 ml dimethylformamide, ethyl bromide (918 μl, 12 mmol) and sodium hydride (282.8 mg, 12 mmol) were added to the reaction mixture. Solution was stirred and refluxed for three hours. The reaction mixture was then evaporated to dryness and washed with water. Pale brown crystals were obtained with 80% yield.

Following the procedure outlined in example 33, but substituting 2,4-dimethoxybenzylaldehyde by 1-ethylindole-3-carboxaldehyde, afforded the [illegible] similar to that of 4-(2,4-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide. Instead of sodium triacetoxyborohydride sodium borohydride was used to reduce the imine intermediate. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.88 (2H, m), 7.52 (1H, m), 7.29 (1H, m), 7.18 (1H, m), 7.05 (1H, m), 7.03 (1H, s), 6.56 (2H, m), 6.52 (1H, s), 4.41 (2H, d, 4.7 Hz), 4.33 (1H, t, 4.7 Hz), 4.08 (2H, q, 7.3 Hz), 2.27 (6H, s), 1.38 (3H, t, 7.3 Hz); MS (ESI$^+$): m/z 458 $(M + Na)^+$.

Example 35

<u>*N*-[4-(4,6-Dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-2-(2-methoxyphenyl)-acetamide</u>

2-Methoxyphenylacetic acid (33 mg, 0.20 mmol) and sulfamethazine (55 mg, 0.20 mmol) were dissolved in 4 ml of chloroform. Triethylamine (70 μl, 0.55 mmol) and diisopropylcarbodiimide (50 μl, 0.20 mmol) were added to the reaction mixture. Solution was stirred and refluxed overnight. The reaction mixture was

then evaporated to dryness, washed with water and purified on silica using gradient elution (chloroform to 2% methanol in chloroform) to obtain white crystals with the yield of 40%. ^{1}H NMR ($CDCl_3$, 500 MHz): 8.04 (2H, m), 7.54 (2H, m), 7.30 (2H, m), 6.98 (2H, m), 6.60 (1H, s), 3.95 (3H, s), 3.72 (2H, s), 2.33 (6H, s); MS (ESI^+): m/z 449 $(M + Na)^+$, 427 $(M + H)^+$.

Example 36

2-Acetyl-*N*-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-benzamide

Following the procedure outlined in example 35, but substituting 2-methoxyphenylacetic acid by 2-acetylbenzoic acid, afforded the title compound with a yield of 11%. MS (ESI^+): m/z 447 $(M + Na)^+$, 425 $(M + H)^+$.

Example 37

1-Methyl-1*H*-indole-2-carboxylic acid [4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-amide

Following the procedure outlined in example 35, but substituting 2-methoxyphenylacetic acid by 1-methylindole-2-carboxylic acid and using dimethylformamide as a solvent afforded the title compound with a yield similar to that of *N*-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-2-(2-methoxyphenyl)-acetamide. MS (ESI^+): m/z 458 $(M + Na)^+$.

Example 38

2-(3,5-Dimethoxyphenyl)-*N*-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-acetamide

Following the procedure outlined in example 35, but substituting 2-methoxyphenylacetic acid by 3,5-dimethoxyphenylacetic acid, afforded the title compound with a yield of 54%. MS (ESI^+): m/z 457 $(M + H)^+$.

Example 39

N-(4,6-Dimethylpyrimidin-2-yl)-4-[2-(2-methoxyphenyl)-ethylamino]-benzenesulfonamide (Compound G)

33 mg (0.08 mmol) *N*-[4-(4,6-dimethylpyrimidin-2-ylsulfomoyl)-phenyl]-2-(2-methoxyphenyl)-acetamide was dissolved in 2 ml tetrahydrofurane. [illegible] borane tetrahydrofurane complex was added to the reaction mixture under nitrogen atmosphere and solution was stirred overnight with reflux. Reaction was quenched with 6 M HCl and the reaction mixture was neutralised with 1 M NaOH. Product was extracted with chloroform and purified on silica using gradient elution (chloroform to 2% methanol in chloroform) to obtain white crystals with a yield of 20%. ^1H NMR ($CDCl_3$, 500 MHz): 7.92 (2H, m), 7.22 (1H, m), 7.12 (1H, m), 6.89 (2H, m), 6.60 (1H, br, s), 6.54 (2H, m), 3.85 (3H, s), 3.38 (2H, t, 6.9 Hz), 2.93 (2H, t, 6.9 Hz), 2.33 (6H, s); MS (ESI^+): m/z 435 $(M + Na)^+$, 413 $(M + H)^+$.

Example 40

4-[2-(3,5-Dimethoxyphenyl)-ethylamino]-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

Following the procedure outlined in example 39, but substituting *N*-[4_(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-2-(2-methoxyphenyl)-acetamide by 2-(3,5-dimethoxyphenyl)-N-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-acetamide, afforded the title compound with a yield of 11%. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.92 (2H, m), 6.58 (1H, s), 6.54 (2H, m), 6.34 (3H, s), 4.20 (1H, t, 5.8 Hz), 3.76 (6H, s), 3.42 (2H, m), 2.85 (2H, t, 6.9 Hz), 2.34 (6H, s); MS (ESI$^+$): m/z 465 $(M + Na)^+$, 443 $(M + H)^+$.

Example 41

4-(Benzhydrylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide (Compound H)

Sulfamethazine (105 mg, 0.38 mmol) and diphenylchloromethane (77 µl, 0.38 mmol) were dissolved in 3 ml pyridine. Solution was stirred and refluxed overnight. The reaction mixture was evaporated to dryness and dissolved to 1 M NaOH. Product was precipitated with 1 M acetic acid. Precipitation cycle was repeated for three times to give white crystals of the title compound with a yield of 8%. MS (ESI$^+$): m/z 467$(M + Na)^+$, 445 $(M + H)^+$.

Example 42

4-(4-Aminobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

18 mg (0.04 mmol) of *N*-(4,6-dimethylpyrimidin-2-yl)-4-(4-nitrobenzylamino)-benzenesulfonamide was dissolved in 1 ml of tetrahydrofurane. Hydrazinium

hydrate (50 μl, 1.5 mmol) and catalytic amount of palladium on charcoal were added to the reaction mixture. Solution was stirred overnight. The reaction mixture was evaporated to dryness and purified on silica using gradient elution (chloroform to 4% methanol in chloroform) to obtain with a yield of 59%. MS (ESI^+): m/z 406 $(M + H)^+$, 384 $(M + H)^+$.

Example 43

4-{[4-(4,6-Dimethylpyrimidin-2-ylsulfamoyl)-phenylamino]-methyl}-benzamide

4-{[4-(4,6-Dimethylpyrimidin-2-ylsulfamoyl)-phenylamino]-methyl}-benzoic acid methyl ester was prepared like described on example 11 and was treated with 25% ammonia to obtain the title compound with a yield lower than 1%. ^1H NMR ($CDCl_3$, 500 MHz): 7.81 (2H, m), 7.67 (2H, m), 7.37 (2H, m), 7.12 (1H, br, t, 6.0

412 $(M + H)^+$.

Example 44

4-{[(2,6-Dichloro-phenyl)-hydroxy-methyl]-amino}-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide

11 mg (0.02 mmol) of 2,6-dichloro-*N*-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-benzamide was dissolved in 2 ml tetrahydrofurane. Lithium aluminium hydride (6 mg, 0.16 mmol) was added to the reaction mixture under nitrogen atmosphere and solution was stirred overnight. The reaction mixture was filtered, evaporated to dryness and purified by on silica using gradient elution (chloroform to 4% methanol in chloroform) to obtain the title compound with a yield of 18%. MS (ESI^+): m/z 475 $(M + Na)^+$.

It will be appreciated that the methods of the present invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent for the specialist in the field that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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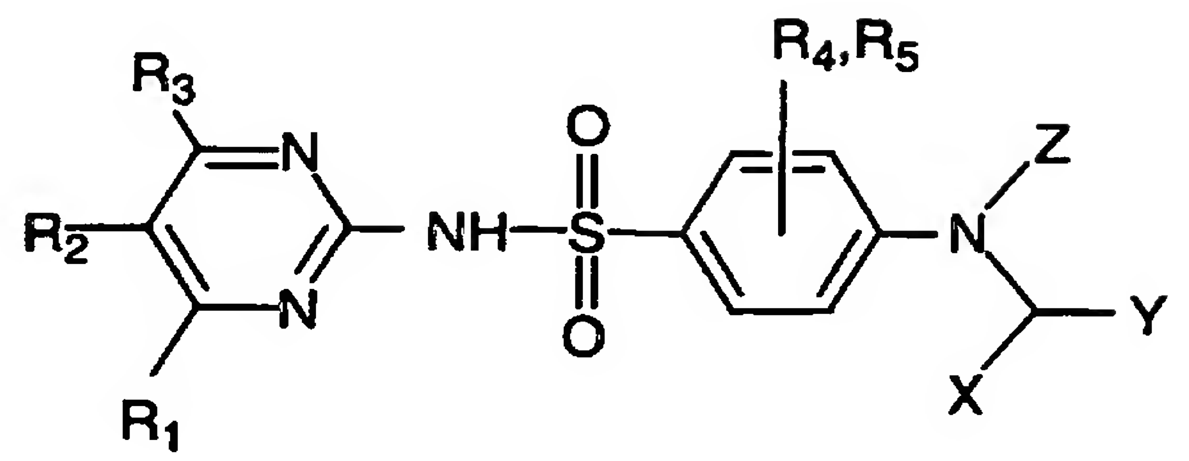
CLAIMS

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof wherein

R_1, **R_2**, **R_3**, **R_4** and **R_5** are independently of each other H, a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen;

X is H, a straight or branched alkyl chain with 1 to 4 carbon atoms, phenyl or

Z is H, acetyl, $-CH_2$-Ph-O-CF_3 or $-CH_2$-Ph-CF_3, were Ph is phenyl;

Y is a ring structure optionally linked to formula (I) with an alkyl chain having one or two carbon atoms, wherein the ring structure is

a) phenyl optionally mono- or disubstituted and each substituent is independently selected from the group consisting of a halogen, a straight or branched alkyl or alkoxy chain with 1 to 4 carbon atoms, a halogen substituted methyl or methoxy group, a nitrile, an amide, amino, or a nitro group;

b) 2-benzimidazolyl, 2-imidazolyl, or 2- or 3-indolyl, wherein one N optionally has a substituent that is a straight or branched alkyl or alkoxy chain with 1 to 4 carbon atoms, or benzyl; and wherein the 2-benzimidazolyl, 2-imidazolyl, or 2- or 3-indolyl is optionally mono- or

disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen;

(c) pyridinyl optionally mono- or disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen; or

(d) naphthyl optionally mono- or disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen;

excluding 4-[(1*H*-benzimidazol-2-ylmethyl)-amino]-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-methyl-1*H*-benzimidazol-2-ylmethyl)-amino]-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-ethyl-1*H*-benzimidazol-2-ylmethyl)-amino]-benzenesulfonamide and *N*-(4-methyl-2-pyrimidinyl)-4-[(1*H*-benzimidazol-2-ylmethyl)-amino]-benzenesulfonamide.

2. A compound of formula (I) according to claim 1 wherein $\mathbf{R_1}$ and $\mathbf{R_3}$ are methyl and $\mathbf{R_2}$, $\mathbf{R_4}$ and $\mathbf{R_5}$ are H.

3. A compound of formula (I) according to claim 1 or 2 wherein **X** is H, **Y** is a phenyl optionally mono- or disubstituted with a straight or branched alkoxy group and **Z** is H.

4. A compound of formula (I) according to claim 2 and 3 wherein said phenyl is substituted and said alkoxy substituent is methoxy selected from the group consisting of 4-(2,4-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(3-methoxybenzylamino)-benzenesulfonamide, 4-(3,5-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-

benzenesulfonamide, 4-(2,5-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide and *N*-(4,6-dimethylpyrimidin-2-yl)-4-(2-methoxybenzyl-amino)-benzenesulfonamide.

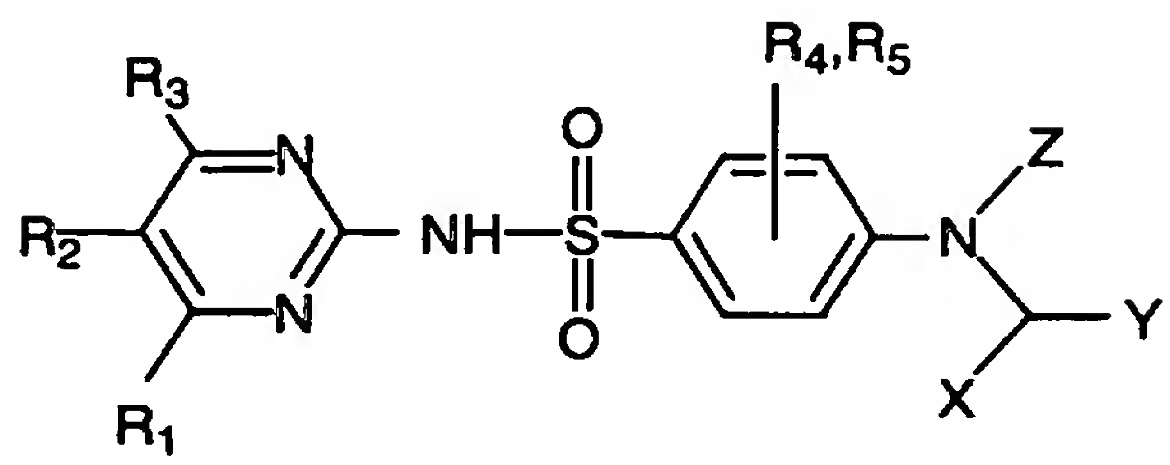
5. A compound of formula (I) according to claim 1 or 2 wherein **X** is H, **Y** is a phenyl optionally mono- or disubstituted with a straight or branched alkyl and/or a halogen and **Z** is H.

6. A compound of formula (I) according to claim 2 and 5 wherein said compound is selected from the group consisting of 4-benzylamino-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(2-methylbenzylamino)-benzenesulfonamide, 4-(2,4-dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(3-methylbenzylamino)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-

N-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, 4-(2,6-dimethylbenzyl-amino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, 4-(4-bromo-benzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide and 4-(2,6-dichlorobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide.

7. A compound of formula (I) according to claim 2 selected from the group consisting of *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-ethyl-1*H*-indol-3-ylmethyl)-amino]-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-isobutyl-1*H*-benzimidazol-2-ylmethyl)-amino] -benzenesulfonamide, *N*-(4,6-dimeth-ylpyrimidin-2-yl)-4-(1-phenylethylamino)-benzenesulfonamide, *N*-(4,6-dimethyl-pyrimidin-2-yl)-4-[2-(2-methoxyphenyl)-ethylamino]-benzenesulfonamide and *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(naphthalen-2-ylmethyl)-amino]-benzene-sulfonamide.

8. Use of a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical preparation useful for the treatment or prevention of a disease mediated by the alpha-2B-adrenoceptor in a mammal wherein

R_1, **R_2**, **R_3**, **R_4** and **R_5** are independently of each other H, a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen;

X is H, a straight or branched alkyl chain with 1 to 4 carbon atoms, phenyl or -OH or =O ;

Z is H, acetyl, $-CH_2$-Ph-O-CF_3 or $-CH_2$-Ph-CF_3, were Ph is phenyl;

Y is a ring structure optionally linked to formula (I) with an alkyl chain having one or two carbon atoms, wherein the ring structure is

a) phenyl optionally mono- or disubstitued and each substituent is independently selected from the group consisting of a halogen, a straight or branched alkyl or alkoxy chain with 1 to 4 carbon atoms, a halogen substituted methyl or methoxy group, an acetyl, a nitrile, an amide, amino, or a nitro group;

b) 2-benzimidazolyl, 2-imidazolyl, or 2- or 3-indolyl, wherein one N optionally has a substituent that is a straight or branched alkyl or alkoxy chain with 1 to 4 carbon atoms, or benzyl; and wherein the 2-benzimidazolyl, 2-imidazolyl or 2- or 3-indolyl is optionally mono- or

disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen;

(c) pyridinyl optionally mono- or disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen; or

(d) naphthyl optionally mono- or disubstituted and each substituent can independently be a straight or branched alkyl or alkoxy group with 1 to 4 carbon atoms, or a halogen;

excluding *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-methyl-1*H*-benzimidazol-2-ylmethyl)-amino] -benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-ethyl-1*H*-benzimidazol-2-ylmethyl)-amino] -benzenesulfonamide and *N*-[4-(4,6-dimethylpyrimidin-2-ylsulfamoyl)-phenyl]-4-ethoxy-benzamide.

according to claim 8 wherein $\mathbf{R_1}$ and $\mathbf{R_3}$ are methyl and $\mathbf{R_2}$, $\mathbf{R_4}$ and $\mathbf{R_5}$ are H.

10. Use of compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 8 or 9 wherein **X** is H , **Y** is a phenyl optionally mono- or disubstituted with a straight or branched alkoxy group and **Z** is H .

11. Use of compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 9 and 10 wherein said phenyl is substituted and said alkoxy substituent is methoxy and said compound is selected from the group consisting of 4-(2,4-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(3-methoxybenzylamino)-benzenesulfonamide, 4-(3,5-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzene-

sulfonamide, 4-(2,5-dimethoxybenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide and *N*-(4,6-dimethylpyrimidin-2-yl)-4-(2-methoxybenzylamino)-benzenesulfonamide.

12. Use of compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 8 or 9 wherein **X** is H, **Y** is a phenyl optionally mono- or disubstituted with a straight or branched alkyl and/or a halogen, and **Z** is H.

13. Use of compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 9 and 12 wherein said compound is selected from the group consisting of 4-benzylamino-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(2-methylbenzylamino)-benzenesulfonamide, 4-(2,4-dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(3-methylbenzylamino)-benzenesulfonamide, 4-(2,5-dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, 4-(2,6-dimethylbenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, 4-(4-bromobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide and 4-(2,6-dichlorobenzylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof according to claim 9 wherein said compound is selected from the group consisting of 4-[(1*H*-benzimidazol-2-ylmethyl)-amino]-*N*-(4,6-dimethylpyrimidin-2-yl)-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-ethyl-1*H*-indol-3-ylmethyl)-amino]-benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(1-isobutyl-1*H*-benzimidazol-2-ylmethyl)-amino] -benzenesulfonamide, *N*-(4,6-dimethylpyrimidin-2-yl)-4-(1-phenylethylamino)-benzenesulfonamide, *N*-(4,6-

dimethylpyrimidin-2-yl)-4-[2-(2-methoxyphenyl)-ethylamino]-benzenesulfonamide and *N*-(4,6-dimethylpyrimidin-2-yl)-4-[(naphthalen-2-ylmethyl)-amino]-benzenesulfonamide.

15. The use according to any of claims 8 to 14, wherein the disease is a coronary heart disease (CHD).

16. The use according to any of claims 8 to 14, wherein the disease is
- acute myocardial infarction (AMI),
- unstable angina pectoris,
- Prinzmetal's variant form of angina pectoris,
- other forms of chronic angina pectoris and CHD, or
- restenosis after coronary angioplasty.

17. The use according to any of claims 8 to 14, wherein the disease is essential hypertension.

18. The use according to any of claims 8 to 14, wherein the disease is a vascular disesase, which is

vasoconstriction or hypoxic brain damage subsequent to subarachnoid haemorrhage,

migraine,

Raynaud's disease or cold intolerance,

pre-eclampsia,

male erectile dysfunction, or

obesity.

19. The use according to any of claims 8 to 14, wherein said alpha-2B-adrenoceptor antagonist is administered to a mammal to potentiate the clinical efficacy of an anaesthetic and/or analgetic alpha-2-adrenoceptor agonist, said agonist not being selective for the alpha-2B-adrenoceptor subtype.

20. The use according to any of claims 8 to 14, wherein said alpha-2B-adrenoceptor antagonist is administered to an individual having a deletion of 3 glutamates from the glutamic acid repeat element of 12 glutamates (amino acids 297–309), in an acid stretch of 17 amino acids, located in the third intracellular loop of the receptor polypeptide.

21. The use according to claim 20 wherein said individual is a deletion/deletion genotype.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FI 02/00643

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/69 C07D403/12 A61K31/635 A61P9/10 A61P9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 58454 A (OY JUVANTIA PHARMA LTD) 16 August 2001 (2001-08-16) the whole document ---	1-21
P,X	DATABASE STN INTERNATIONAL [Online] FILE CAPLUS; SANKYO COMPANY LTD: "Preparation of nitrophenylcarboxamide derivatives as ... retrieved from CAPLUS, accession no. 2001:816614 Database accession no. 135:357944 XP002902751 abstract & WO 01 83427 A (SANKYO COMPANY LTD) 8 November 2001 (2001-11-08) --- -/--	1-21

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

15 October 2002

Date of mailing of the international search report

01 11. 2002

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INTERNATIONAL SEARCH REPORT

I onal Application No
PCT/FI 02/00643

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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